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CHASE J. TROMBELLA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Warren Hoeffler

Serial No.: 09/622,703

Filing Date: August 21, 2000

For: METHOD FOR DETERMINING TRANSCRIPTION FACTOR ACTIVITY AND ITS TECHNICAL USES

Examiner: A. K. Chakrabarti

Group Art Unit: 1655

RESPONSE TO OFFICE ACTION MAILED DECEMBER 5, 2001, PAPER NO. 5

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is in response to the Office Action dated December 5, 2001, Paper No. 5, for which a response is due on March 5, 2002. A petition for a one month extension of time is enclosed to extend the deadline to respond to this Office Action from March 5, 2002 to April 5, 2002. As such, this response is timely filed.

AMENDMENTS

In the Claims:

1. (Reiterated) A method of detecting transcription activity comprising detecting the presence or absence of a nick in a DNA molecule, wherein the presence of a nick in the DNA molecule indicates transcription activity.

2. (Reiterated) The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is measured by determining the change in electrophoretic mobility of nicked DNA on an electrophoretic gel.

3. (Reiterated) The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a SI nuclease assay.

4. (Reiterated) The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a primer extension reaction.

5. (Reiterated) The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a polymerase chain reaction amplification reaction.

6. (Reiterated) The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a DNA sequencing assay.

7. (Reiterated) The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a protein binding assay.

8. (Reiterated) The method of claim 1 wherein the DNA is affixed to a matrix.

9. (Reiterated) The method of claim 8 wherein the matrix is a biological chip.

10. (Reiterated) A method of detecting transcription activity comprising the steps of :

a) providing a DNA template comprising at least one binding region for a transcription factor;

b) contacting the DNA template with at least one transcription factor; and

c) detecting the presence or absence of a nick in the DNA template, wherein the presence of a nick in the DNA template indicates transcription activity.

11. (Reiterated) The method of claim 10, wherein the transcription factor is in a nuclear cell extract.

12. (Reiterated) The method of claim 10, wherein the DNA template is inserted into a viral or plasmid vector and introduced into a cell.

13. (Reiterated) The method of claim 10, wherein the DNA template is fixed to a matrix.

14. (Reiterated) The method of claim 13, wherein the matrix is a biological chip.

Please CANCEL claims 15-~~55~~ 47 without prejudice or disclaimer.

REMARKS

Reconsideration is respectfully requested. Claims 15-55 have been cancelled without prejudice or disclaimer to filing claims to this subject matter in one or more divisional or continuation applications. Claims 1-14 have been rejected. Claims 1-14 are pending.

Restriction/Election

Applicant affirms the election to prosecute Group I, claims 1-14, without traverse, and reserves the right to prosecute claims 15-55 in future applications.

Claim Rejections - 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-2, 4-8, and 10-13 under 35 U.S.C. § 102(b) as being anticipated by Gansz, et al. (Molecular and General Genetics, (1991), Vol. 225, 427-434).

The Claimed Invention

Applicant's claims methods of detecting transcription activity comprising contacting a DNA template with at least one transcription factor, and detecting the presence of a nick in a DNA molecule, wherein the presence of the nick indicates transcription activity. The nick in the

DNA serves as an entry site for an RNA polymerase complex. The complex migrates down the DNA to the transcription start site where transcription is initiated. Dependent claims include the method wherein the nick is detected by an electrophoretic gel, primer extension reaction, PCR amplification reaction, DNA sequencing assay, and protein binding assay. Additional dependent claims are directed to the method wherein the DNA is affixed to a gel matrix, the transcription factor is in a nuclear cell extract, and the DNA template is inserted into a viral or plasmid vector and introduced into a cell.

The Prior Art

Gansz, et al. disclose a bacterial phage (virus) transcription factor, DsbA, that binds late transcription promoters, and also nicks DNA.

Examiner's Argument

The Examiner alleges that Gansz, et al. teach a) providing a DNA template comprising at least one binding region for a transcription factor, b) contacting the DNA template with at least one transcription factor, and c) detecting the presence or absence of a nick in a DNA template, where the presence of a nick indicates transcription. The Examiner further alleges that the reference teaches determining the presence of a nick by electrophoretic ability, in a sequencing assay, in a primer extension reaction, by PCR amplification, and in a protein binding assay. The Examiner alleges that Gansz, et al. teach a method wherein the DNA is affixed to a gel matrix and wherein the transcription factor is in a nuclear cell extract. Finally, the Examiner alleges that Gansz, et al. teach the method wherein the DNA is inserted into a viral vector and introduced into a cell.

The Prior Art Distinguished

Applicant respectfully traverses the rejection.

1. Lack of Correlation between Nicking and Transcription

Gansz, et al. teach a gene product that binds, and separately causes nicks in, a double stranded DNA molecule, but any similarity to the claimed invention ends here. Gansz, et al. fail to teach or disclose a method of detecting transcription activity by identifying nicks in a DNA molecule. Further, Gansz, et al. do not teach that the presence of the nicked DNA indicates transcriptional activity, and only speculate as to the reasons behind the DNA nicks. Finally, the reference fails to disclose detecting the presence or absence of a nick related to transcription.

While Gansz, et al. teach a transcription factor that separately nicks DNA, the reference fails to teach any correlation between DsbA nicking and transcription, let alone that DNA nicks can be used to detect actual transcription. The authors instead find their functional assay results inconclusive as to the role of nicking. Gansz, et al. state that that "surprisingly, the nicks occur on the template strand and must separate the promoter from downstream structural genes," for which the authors explicitly "*have no explanation*." (Results and Discussion, page 433, paragraph 1, *emphasis added*). The authors speculate that the observed DNA cleavage "*might* be an *artificial reaction*, occurring only in the absence of certain cofactors or additional reaction partners," or that the protein "*might* remain attached to the cleavage site," or "*might* be responsible for an activated template." [*emphasis added*]. Such speculation hardly demonstrates that nicking has anything to do with transcription activity, or that identification of nicking can be used in a separate method of detecting transcription not disclosed by Gansz, et al. Further, the DNA nicking experiment (Figure 5) detects only that the transcription factor nicks DNA, and does not detect actual transcription based on DNA nicking. Gansz, et al. present nicking by DsbA as a possible property of a particular virus (T4) protein and not as a general property of transcription activating proteins. It is well known that viruses and phages often use unusual

mechanisms to subvert host cells. Gansz, et al. does not suggest or imply nicking as a possible property of any other protein other than the viral protein DsbA.

2. Transcription Detection by Measuring Gene Product Expression

Applicant respectfully notes that the Examiner takes separate and distinct experimental evidence provided by Gansz, et al. to argue that the separate experiments in fact constitute the claimed methods. First, the Examiner specifically asserts that a) the Summary discloses a method of detecting transcription activity. Gansz, et al., however, fail to disclose a method for detecting transcription by detecting nicking in DNA. This method teaches detecting transcription by measuring production of the associated gene product, not by determining whether a nick is present (see Summary, lines 15-17).

3. Gel Retardation Assay

The Examiner further asserts that b) Gansz, et al. teach contacting a DNA with a transcription factor for use in a method of detecting transcription by detecting nicking (Materials and Methods Gel Retardation subsection and Figure 1 and 2). The Gel Retardation Assays cited by the Examiner, however, are used to "identify discrete sequences to which the purified protein might possibly bind," and are not used in a method of detecting transcription by detecting DNA nicking. Further, Figure 1 shows only the cloning strategy for over-expression of the transcription factor, and Figure 2 shows only that the transcription factor preferentially binds late transcription factors. Neither the Gel Retardation Assay nor the Figures disclose, or even hints at, a process to detecting actual transcription by detecting nicking.

4. No Experimental Data Establishes a Connection between Nicking and Transcription

The Examiner further alleges that c) Gansz, et al. use the presence or absence of a nick in the DNA template to indicate transcription activity (Summary, lines 11-12 and the Results and

Discussion section, and Figures 2-5). As discussed *supra*, however, the Results and Discussion section demonstrate no correlation between DsbA's nicking and transcription functions. The Figures also fail to show a method of detecting transcription by detecting nicking. Figure 2 depicts a gel retardation assay showing DNA binding and transcription initiation of the DsbA transcription factor, not identification of actual transcription by detecting DNA nicking. Figure 3 shows a DNA footprint analysis of promoter-DsbA complexes, not transcription, and certainly not detection of transcription by detecting DNA nicking. Figure 4 depicts the effect of DsbA in in vitro run-off transcription by detecting the transcription product, not the presence of DNA nicks. Figure 5 depicts nicking of a double strand vector, but the Figure caption and associated discussion fail to teach a relationship between nicking and transcription, or that the presence or absence of nicking can be used subsequently to detect transcription. Clearly, the reference fails to show that nicking by DsbA bears any correlation to actual transcription activity.

5. DNA Nicking Experiment

In addition, the Examiner alleges that Gansz, et al. disclose a method of detecting transcription by detecting DNA nicking (Figure 5 and the Materials and Methods, DNA footprinting section). As discussed *supra*, however, Figure 5 shows only DNA nicking, not detecting transcription by detecting nicking, and the associated text does not teach any correlation between transcription activity and nicking. The DNAse I footprinting section teaches a method for detecting DNA binding by interference with DNAse I activity, and fails to teach method of detecting transcription by detecting DNA nicking. Gansz, et al. thus fail to teach that changes in electrophoretic mobility may be used to detect transcription activity by detecting nicks in DNA.

6. Primer Extension and PCR Amplification Reactions

The Examiner further asserts that the reference discloses a method of detecting transcription by detecting the presence or absence of nicked DNA via primer extension and PCR amplification reactions (Materials and Methods, DNA Sequencing section). The disclosed methods, however, are directed toward sequencing T4 mutants having early and/or late promoter regions. Further, the DNA fragments generated by the experiment were used in binding assays for DsbA, and were not used to detect transcription by detecting DNA nicking. While the reference teaches conventional PCR techniques, it fails teach use of either a primer extension reaction or PCR in a method of detecting transcription by detecting the presence or absence of a nicking.

7. Protein Binding Assay

In addition, the Examiner asserts that Gansz, et al. teach a method of detecting transcription by detecting nicking via a protein binding assay (Figure 2 and the Results and Discussion, Gel Retardation Assay section). Figure 2 and the associated discussion, however, fail to disclose the use of the assay in a method of detecting actual transcription by detecting the presence or absence of DNA nicking. Instead, the cited text teaches a gel retardation assay in which DsbA binds DNA, and detection of additional transcription factors.

8. Gel Matrix

In addition, the Examiner asserts that Gansz, et al. teach a method of detecting transcription by detecting DNA nicks in a gel matrix (Figures 2-5 and Materials and Methods In vitro transcription assays). While DNA in each of the figures and the methods teach DNA affixed to a gel matrix, the DNA is in the gel matrix for substantially different reasons than as a method of detecting transcription by detecting DNA nicking. Figure 2 demonstrates only DsbA-

DNA binding and transcription-machinery recruitment, not a method of detecting nicking. Figure 3 shows only footprint analysis of preferential promoter binding sites, not transcription or a method of detecting nicking by DsbA. Figure 4 shows in vitro transcription, not a method of detecting transcription by detecting nicking. Figure 5 shows a gel of DNA nicking, not a method of detecting transcription. The Materials and Methods section details how to conduct an in vitro transcription assay in a gel, and does not disclose detecting transcription by detecting nicking. Thus, while each of the sections teach DNA in a gel, no section teaches how to a) detect transcription by b) detecting nicking of DNA fixed in a gel.

9. Nuclear Cell Extract Transcription Factor

Further, the Examiner asserts that the reference teaches a method of detecting transcription by detecting DNA nicking using a transcription factor from a nuclear cell extract (Materials and Methods, Enzyme Protein isolation section). While the reference section teaches isolation of the transcription factor DsbA from a bacterial cell extract, however, DsbA is not used in a method to detect transcription by detecting nicking. Furthermore, the Gasnz, et al. study was conducted in bacterial cells. Bacterial cells are procaryotic and, by definition, do not contain a nucleus. As such, such cells do not contain a nuclear extract. Therefore, Gansz, et al. fail to teach a method of detecting transcription activity by detecting DNA nicks wherein the transcription factor is a nuclear cell extract.

10. Viral Vectors

Finally, the Examiner alleges that Gansz, et al. teach a method of inserting a method of detecting transcription by detecting DNA nicks wherein the DNA template is inserted into a viral vector and introduced to a cell (Figure 1 and the Cloning and Over-expression subsections of the Results and Discussion). While the cited section of the Gansz, et al. reference teaches inserting a

DNA template into a vector and inserting it into a cell, these were only conventional methods of cloning *dsbA* and over-expressing the gene product DsbA, and remain entirely unassociated with any method of detecting transcription.

11. Conclusion

In view of the foregoing, Applicant respectfully requests that the rejection under 35 U.S.C. §102(b) be withdrawn.

Claim Rejections - 35 U.S.C. § 103 -

Gansz, et al. in view of Mirzabekov, et al. (U.S. Patent No. 5,851,772)

Claims 1-2 and 4-14 have been rejected over 35 U.S.C. § 103 as being obvious over by Gansz, et al. in view of U.S. Patent No. 5,851,772 (Mirzabekov, et al.).

The Claimed Invention

Applicant claims a method of detecting transcription activity comprising detecting a the presence of absence of a nick in a DNA molecule, wherein the presence or absence of the nick indicates transcription activity. Nicks may be detected using a number of experimental methods, including electrophoretic gels, primer extension reaction, PCR, DNA sequencing assays, and protein binding assays. The DNA may be fixed to a matrix, biological chip, or inserted into a viral or plasmid vector and introduced into a cell. The transcription factor may be from a nuclear cell extract.

The Prior Art

Gansz, et al.

Gansz, et al. disclose a phage transcription factor, DsbA, that binds late transcription promoters, and also nicks DNA in bacterial cells lacking a nucleus.

Mirzabekov, et al.

Mirzabekov, et al. teach DNA-array based methods of identifying and enriching DNA sequences by hybridization.

Examiner's Argument

The Examiner alleges that Gansz, et al. teach a method of detecting transcription activity comprising the steps of providing a DNA template comprising at least one binding region for a transcription factor, and detecting DNA nicking. The Examiner further alleges that Mirzabekov, et al. teach the method wherein the DNA is affixed to a biological chip. The Examiner asserts that it would have been obvious for one of ordinary skill in the art to combine the teachings of Gansz, et al. and Mirzabekov, et al. since Mirazbekov, et al. state that an object of the invention is to "provide an easy method for identifying and subsequently enriching specific DNA sequences," that their invention facilitates use of a large number of oligomers "to isolate ...target sequences on DNA," and "pinpoint desired DNA sequences." Finally, the Examiner states that an ordinary practitioner would have been motivated to combine the references in order to a) improve transcription activity to detect a large number of DNA molecules in a short period of time, b) achieve the express advantages of easily identifying and subsequently enriching specific DNA sequences, c) exploit the ease of use of a large number of oligomers, d) isolate the target sequences contained on ssDNA, and e) achieve the advantage of a method that provides a dramatic reduction in the required number of immobilized oligomers to pinpoint desired DNA sequences.

The Prior Art Distinguished

35 U.S.C. § 103(a) requires that "...differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The *prima facie* case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

Applicant respectfully traverses this rejection, since neither reference teaches the elements of the claimed methods, both fail, individually or in combination, to provide the requisite motivation or suggestion to combine references, and one of ordinary skill in the art would not expect to modify or combine the teachings to practice the instant invention with a reasonable expectation of success.

1. Failure to Teach All Claim Limitations

For the reasons stated *supra* in the response to the 35 U.S.C. § 102 rejection, Gansz, et al. fail to teach a method of detecting transcription activity by contacting a DNA template with a transcription factor, and detecting nicking using any of the claimed experimental techniques.

Mirzabekov, et al. also fail to teach a gene chip capable of use to identify DNA nicks. While Mirzabekov, et al. teach a gene chip used in methods of detecting and enriching DNA sequences by hybridization, the reference fails to make any reference whatsoever to identification of nicked DNA. The Examiner cites Mirzabekov, et al. col. 2 lines 43-53, to support the use of a biological chip to identify DNA nicks. The cited passage, however, discloses a method of identifying and immobilizing DNA sequences complementary to ssDNA target sequences. The claimed invention, by contrast, is directed to a method of identifying transcription by detecting nicks in DNA, and not to detecting specific sequences or enriching DNA. Mirzabekov, et al. provide no teaching, guidance, or reference to DNA nicking, let alone

detecting transcription by locating nicks in DNA. Since the reference is directed exclusively to identifying specific DNA sequences on a gene chip, and the claimed invention has nothing to do with identifying specific DNA sequences on a gene chip, Mirzabekov, et al. fail to teach a chip used in Applicant's claimed methods.

2. Lack of Motivation or Suggestion to Combine

The cited references also fail to provide motivation or suggestion to combine their teachings and perform the claimed methods. First, the Examiner asserts that Mirzabekov, et al. provide motivation to combine the references in order to improve the transcription activity detection in a short period of time. The reference, however, lacks any support for this motivation, and instead provides only the motivation to detect specific, complementary sequences and enrich DNA having particular sequences. As already noted, the instant invention is directed to detecting transcription by detecting DNA nicks, and sequence plays no role in the detection. Second, the Examiner asserts that Mirzabekov, et al. provide motivation or suggestion to combine the references by disclosing an easy method of identifying and enriching specific nucleic acids. These methods, however, only related to identifying specific sequences by hybridization, and have nothing to do with the claimed method of detecting transcription by detecting nicks in DNA. Third, the Examiner asserts that Mirzabekov, et al. provide a motivation or suggestion to combine by presenting easy methods of identifying and enriching specific sequences on a chip. Applicant's claimed invention, however, does not require identification or enrichment of specific sequences, only identification of DNA nicks absent any enrichment. Fourth, the Examiner asserts that Mirzabekov, et al. provides motivation to combine the references in order to isolate target sequences contained on ssDNA. Applicant's claimed method, however, would not be aided by isolating target sequences, since the method identifies

nicked DNA. Finally, the Examiner asserts that Mirzabekov, et al. provide the requisite motivation or suggestion to provide a dramatic reduction in the required number of immobilized oligomers and pinpoint a desired sequence. Again, pinpointing a specific DNA sequence has nothing to do with the claimed invention directed to detecting transcription by detecting nicked DNA.

3. Reasonable Expectation of Success

One of ordinary skill in the art would not have a reasonable expectation of success in combining the cited prior art to make the claimed invention, since the references teach away from the present invention. Gansz, et al. fails to teach any correlation between DsbA nicking and transcription, let alone that DNA nicks can be used to detect actual transcription. The authors instead speculate broadly as to the role of nicking. Gansz, et al. state that "surprisingly, the nicks occur on the template strand and must separate the promoter from downstream structural genes," for which the authors explicitly "*have no explanation*." (Results and Discussion, page 433, paragraph 1, *emphasis added*). The authors speculate that the observed DNA cleavage "*might* be an *artificial reaction*, occurring only in the absence of certain cofactors or additional reaction partners," or that the protein "*might* remain attached to the cleavage site," or "*might* be responsible for an activated template." [*emphasis added*]. Such speculation hardly demonstrates that nicking has anything to do with transcription activity, or that identification of nicking can be used in a separate method of detecting transcription not disclosed by Gansz, et al. Further, the DNA nicking experiment (Figure 5) detects only that the transcription factor nicks DNA, and does not teach, suggest, or even hint at detecting actual transcription from DNA nicks. Mirzabekov, et al. also fail to provide any hint at detecting transcription by detecting nicking.

4. Conclusion

The Examiner must satisfy the *prima facie* burden of proving obviousness by showing that the prior art contains every element of the invention, that one of ordinary skill in the art would have been motivated to combine the references, and that one of ordinary skill in the art would have a reasonable expectation of success. The Examiner fails to satisfy this burden.

In view of the foregoing, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

Claim Rejections - 35 U.S.C. § 103 -

Gansz, et al. in view of Hodgson, et al. (U.S. Patent No. 5,854,020)

The Examiner has rejected claims 1-8 and 10-13 have been rejected over 35 U.S.C. § 103 as being obvious over by Gansz, et al. in view of Hodgson, et al. (U.S. Patent No. 5,854,020).

The Claimed Invention

Applicant claims a method of detecting transcription activity comprising detecting the presence or absence of a nick in a DNA molecule, wherein the presence or absence of the nick indicates transcription activity. Nicks may be detected using a number of experimental methods, including electrophoretic gels, S1 nuclease assay, primer extension reaction, PCR, DNA sequencing assays, and protein binding assays. The DNA may be fixed to a matrix, or inserted into a viral or plasmid vector and introduced into a cell. The transcription factor may be from a nuclear cell extract.

The Prior Art

Gansz, et al.

Gansz, et al. disclose a phage transcription factor, DsbA, that binds late transcription promoters, and also nicks DNA.

Hodgson, et al.

Hodgson, et al. teach that S1 nuclease can be used to identify promoter sequences.

Examiner's Argument

The Examiner alleges that the Gansz, et al. teach a method of detecting transcription activity by contacting DNA with a transcription factor and detecting nicking, and Hodgson, et al. teach a method wherein the transcription initiation site is determined by an S1 nuclease assay.

The Prior Art Distinguished

Applicant respectfully traverses this rejection, since a) neither reference teaches the elements of the claimed methods, b) both fail, either individually or in combination, to provide the requisite motivation or suggestion to combine references, and c) one of ordinary skill in the art would not expect to modify or combine the teachings to practice the instant invention with a reasonable expectation of success.

1. Failure to teach all claim limitations

For the reasons stated *supra* in the response to the 35 U.S.C. § 102 rejection, Gansz, et al. fail to teach a method of detecting transcription activity by detecting nicking using any of the claimed experimental techniques.

Hodgson, et al. fail to teach a method using an S1 nuclease assay to identify DNA nicking. As disclosed by Hodgson, et al., the S1 nuclease assay identifies a transcription initiation promoter sequence located specifically at the start site of transcription. In claim 3,

Applicant's claimed invention, however, is directed to a method of using S1 nuclease to determine the presence or absence of DNA nicks. The nicks detected by the present invention are generally located at or near the binding sites of transcription factors within promoter regions and not necessarily located at the initiation promoter sequence. Since the referenced method does not use S1 nuclease in the manner of the claimed invention, Hodgson, et al. fails to meet the claim limitation.

2. Lack of Motivation or Suggestion to Combine

The cited references also fail to provide motivation to combine the references to achieve the claimed methods. The Examiner first asserts that one of ordinary skill in the art would have been motivated to use the S1 nuclease to identify transcription activity by identifying nicks, since column 5, lines 22-24 state that "within the promoter sequence will be found a transcription initiation site conveniently defined by mapping with nuclease S1." An ordinary practitioner, however, would only be motivated to identify transcription initiation sites, not DNA nicks as claimed since the claimed method is directed to identifying transcription by identifying a DNA nick, not by identifying a transcription initiation site. Second, the Examiner asserts that Hodgson, et al. provide the motivation of finding a transcription initiation site. The claimed invention, however, is directed to identifying nicks which represent entry sites for the RNA polymerase complex as part of the transcription process, not possible transcription initiation sites. Accordingly, the reference cited by the Examiner fails to provide the requisite motivation to combine the references.

3. Reasonable Expectation of Success

One of ordinary skill in the art would not have a reasonable expectation of success in combining the cited prior art to make the claimed invention, since the references teach away

from the present invention. Gansz, et al. fails to teach any correlation between DsbA nicking and transcription, let alone that DNA nicks can be used to detect entry sites for RNA poplymerase complexes as initiation of the transcription process. The authors instead speculate broadly as to the role of nicking. Gansz, et al. state that that "surprisingly, the nicks occur on the template strand and must separate the promoter from downstream structural genes," for which the authors explicitly "*have no explanation.*" (Results and Discussion, page 433, paragraph 1, *emphasis added*). The authors speculate that the observed DNA cleavage "*might* be an *artificial reaction*, occurring only in the absence of certain cofactors or additional reaction partners," or that the protein "*might* remain attached to the cleavage site," or "*might* be responsible for an activated template." [*emphasis added*]. Such speculation hardly demonstrates that nicking has anything to do with transcription activity, or that identification of nicking can be used in a separate method of detecting transcription not disclosed by Gansz, et al. Further, the DNA nicking experiment (Figure 5) detects only that the transcription factor nicks DNA, and does not teach, suggest, or even hint at detecting actual transcription from DNA nicks. Hodgson, et al. also fail to provide any hint at detecting transcription by detecting nicking.

4. Conclusion

The Examiner must satisfy the *prima facie* burden of proving obviousness by showing that the prior art contains every element of the invention, that one of ordinary skill in the art would have been motivated to combine the references, and that one of ordinary skill in the art would have a reasonable expectation of success. The Examiner fails to satisfy this burden.

In view of the foregoing, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

Conclusion

In view of the foregoing, Applicant believes all claims now pending are in condition for allowance. Reconsideration and a Notice of Allowance are respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 268-6237.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 50656 2000200.

Respectfully submitted,

Dated: April 5, 2002

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